REMARKS

Claims 1-69 are all the claims pending in the application. Claims 4-9, 11, 12, 14, 15, 17, 18, 20, 21, 23, 24, 26, 27, and 29-69 have been withdrawn from consideration; claims 1-3, 10, 13, 16, 19, 22, 25 and 28 have been rejected.

The specification has been amended to correct an error in the legend of Fig. 3(A). The sequence for the BAD BH3 domain shown in Fig. 3(A) is residues 106-131 of human BAD, recited in SEQ ID NO: 4 (supported by the Sequence Listing). Thus the second line of the figure legend has been corrected to state that alignment against the "human" BAD BH3 domain is shown, and that the sequence is that of SEQ ID NO: 4. Further, the "longer murine BAD" is incorrectly identified in the figure legend as "SEQ ID NO: 1." Therefore, the sequence identifier for longer murine BAD has been corrected to recite "SEQ ID NO: 2" (for support, see, e.g., page 7, line 11).

The specification has also been amended to add sequence identifiers to the legend for Fig. 3(B). Residues 143-168 of the BAD BH3 domain mentioned at line 5, page 32, are residues 143-168 of SEQ ID NO: 2 (see page 76, lines 18-23, for support). Thus, the sequence identifier "SEQ ID NO: 2" has been added to lines 5 and 6, page 32, of the specification. Similarly, residues 71-89 correspond to residues 1-20 of SEQ ID NO: 5 (the residues in SEQ ID NO: 5 correspond to residues 71-95 of human BAK), and the figure legend has been amended accordingly.

Claims 1, 2 and 13 have been amended to replace the term "substantially identical" with "at least 75% homologous." Support for the amendment may be found at page 45, lines 13-16, of the specification.

I. Sequence Rule Compliance

At page 2 of the Office Action, the Examiner states that reference to sequences comprising residues 71-89 and 143-168, in the legend of Fig. 3B, is not accompanied by sequence identification numbers.

In response, Applicants submit herewith an amended legend for Fig. 3B. Residues 71-89 of human BAK are now said to correspond to residues 1-20 of SEQ ID NO: 5 (SEQ ID NO: 5 comprises residues 71-95 of human BAK protein). Similarly, residues 143-168 of human BAD are now said to correspond to those residues set forth in SEQ ID NO: 4.

Accordingly, Applicants respectfully request reconsideration and withdrawal of this objection.

II. Objection

At page 2 of the Office Action, the Examiner objects to the specification because the BAD BH3 sequence (SEQ ID NO: 4 or BAD sequence in Fig. 3(A)) does not seem to correspond to the residues 143-168 of SEQ ID NO: 1, defined as BAD BH3 peptide in Fig. 3(B) legend on page 32.

In response, Applicants note that the BAD BH3 peptide referred to the figure legend for Fig. 3(B) is residues 143-168 of longer murine BAD (SEQ ID NO: 2). The figure legend has been amended to insert the correct sequence identifier.

III. Rejection of claims under 35 U.S.C. §112, second paragraph

At page 3 of the Office Action, claims 1-3, 10, 13, 16, 19, 22, 25 and 28 are rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite.

A. The Examiner asserts that the use of the term "substantially" in claims 1, 2 and 13 renders the claims indefinite.

In response, Applicants note that the term "substantially identical" is defined at page 45, lines 13-16, of the specification. Therein, it is said to mean at least 75% (and preferably 85%, more preferably 90 to 95%) identity between two or more sequences.

Applicants have amended the claims in which the term occurs to replace "substantially identical" with "at least 75% homologous."

Applicants thus assert that the claims are now clearly definite and respectfully request reconsideration and withdrawal of this rejection.

B. The Examiner further asserts that the use of the designation "BH3" as the sole means of identifying the claimed peptide domain renders claims 1 and 13 indefinite, and that physical or functional characteristics should be used instead.

In response, Applicants note that BH3 is defined as one of the four conserved motifs found in Bcl-2 family members (page 2, line 20 - page 3, line 1), and it is further defined at page 43, lines 5-8, as the amino acids comprising from approximately residues 143-168 of SEQ ID NO: 2, or any portion thereof, or any sequence of amino acids that corresponds to this sequence.

Thus, Applicants assert that the designation "BH3" is clearly defined and therefore definite. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

IV. Rejection of claims under 35 U.S.C. §112, written description

At page 4 of the Office Action, claims 1-2, 10, 13, 16, 19, 22, 25 and 28 are rejected under 35 U.S.C. §112, first paragraph, as lacking adequate written description.

The Examiner is of the opinion that claiming "substantially" identical sequences causes the cited claims to encompass any mutant of SEQ ID NO: 1, or a polypeptide BAD with any mutation in the BH3 domain.

The Examiner asserts that there is little support to indicate which of the amino acid residues could be changed to produce a functional protein. Further, structural features that could distinguish the claimed variants, as well as functional attributes, are not disclosed. The Examiner concludes by stating that only a peptide comprising SEQ ID NO: 1, wherein serine 118 is mutated, but not the full breadth of the claims, meets the written description requirements.

In response, the claims have been amended to include more disclosure regarding the nature of the claimed genus of proteins. As discussed above, the phrase "substantially identical" has been replaced with "at least 75% homologous" to a BH3 domain. Thus, in contrast to the Examiner's statement to the contrary, the claims recite a common structural attribute that identifies the claimed variants.

Because the claims recite both structural ("at least 75% homologous" to a BH3 domain) and functional characteristics ("has cell death promoting activity"), Applicants assert that there is adequate written description for the rejected claims. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection.

V. Rejection of claims under 35 U.S.C. §112, enablement

A. At page 7 of the Office Action, claims 1-2, 10, 13, 16, 19, 22, 25 and 28 are rejected under 35 U.S.C. §112, first paragraph, as lacking adequate enablement.

The Examiner states that the cited claims recite an isolated mutant polypeptide BAD or fragment thereof, which 1) contains a domain substantially identical to BH3 domain of a

naturally-occurring or wild-type mammalian BAD, 2) does not have a serine at a position corresponding to position 118 of SEQ ID NO: 1, wherein "said position is identified by alignment of said isolated polypeptide or fragment thereof to SEQ ID NO: 1," and 3) has cell death promoting activity.

The Examiner states that the specification does not enable the skilled artisan to align sequences for comparison with SEQ ID NO: 1 to identify an amino acid at a position corresponding to serine 118 of SEQ ID NO: 1. Therefore, undue experimentation would be required to practice the claimed invention.

In response, Applicants note that at page 45 of the specification means by which the skilled artisan could compare two sequences are disclosed. Further, the claims have been amended as discussed above to recite "at least 75% homology." Applicants assert that given the teachings in the specification, and the provision that the homology be at least 75%, the skilled artisan would clearly be enabled to practice the current invention within the scope of the claims. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection.

B. At page 9 of the Office Action, claims 1-2, 10, 13, 16, 19, 22, 25 and 28 are rejected under 35 U.S.C. §112, first paragraph, as being non-enabled.

The Examiner states that the scope of the claims includes numerous structural mutants, and that Applicants have not shown how to make and use the claimed mutants which are capable of functioning as that which is being disclosed. The Examiner concludes that in view of the unpredictability, one of skill in the art would be forced into undue experimentation in order to perform the claimed invention as broadly as claimed.

In response, Applicants assert that the present specification provides an enabling disclosure of how the skilled artisan could easily determine whether a candidate protein has cell death promoting activity (pages 86-93 of the specification). Further, in light of the amendment of the claims to recite "at least 75% homology," the skilled artisan would easily be able to determine whether a candidate protein falls within the structural attributes of the claimed invention. As a result, the skilled artisan would be clearly enabled to easily determine whether a candidate protein has the claimed structural and functional attributes of the claimed proteins.

Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

VI. Rejection of claims under 35 U.S.C. §102

At page 11 of the Office Action, claims 1-2, 10, 19, 22, 25 and 28 are rejected under 35 U.S.C. §102(b) as being anticipated by U.S. Pat. No. 5,965,703 ("the '703 patent").

The Examiner states that SEQ ID NO: 3 of the '703 patent (a mouse BAD) falls within the scope of the cited claims because it discloses a protein with 75% homology to SEQ ID NO: 1 of the present invention, with a threonine at a position corresponding to residue 118 of SEQ ID NO: 1, and with cell death promoting activity.

In response, Applicants assert that there is no disclosure in the '703 patent that the protein encoded by SEQ ID NO: 3 (a mouse BAD) therein, has cell death promoting activities. While the cell death promoting activity is described for the human BAD disclosed therein, it is not confirmed for mouse BAD.

As is discussed in the present application, the function of murine BAD is largely mediated by one amino acid (serine 136). The absence of phosphorylation at this site leads to

increased cell death. Thus, a single amino acid change in a BAD protein could abolish the activity of the protein. As shown in Figure 2 of the '703 patent, there are a number of amino acid differences between human and murine BAD. Thus, given only the amino acid sequence of murine BAD, the skilled artisan would not readily expect that it would also have cell death promoting activity, absent some evidence demonstrating such activity.

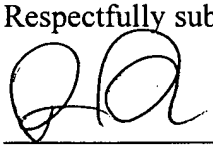
Thus, the '703 patent does not anticipate each element of the claimed invention, and Applicants respectfully request reconsideration and withdrawal of this rejection. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

VII. Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

Applicant hereby petitions for any extension of time which may be required to maintain the pendency of this case, and any required fee, except for the Issue Fee, for such extension is to be charged to Deposit Account No. 19-4880.

Respectfully submitted,



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APPENDIX

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

The specification is changed as follows:

At page 31, the paragraph encompassing lines 13-24 has been amended as follows:

Fig. 3(A) is an amino acid sequence alignment of BH3 domains of the Bcl-family members, against the BH3 domain of human BAD (SEQ ID NO:~~4~~1). The open rectangle, encompassing the closed rectangle, represents the amino acid sequence of the longer murine BAD (SEQ ID NO:~~2~~1) protein. The closed rectangle represents the BH3 domain of the longer murine BAD (SEQ ID NO:~~2~~1) protein. "S112," S136" and "S155" indicate the location of serine residues at positions 112, 136 and 155 of the longer murine BAD (SEQ ID NO:~~2~~1) protein, respectively. The amino acid sequences are those of BAD (SEQ ID NO:4), BAK (SEQ ID NO:5), BAX (SEQ ID NO:6), BIK (SEQ ID NO:7), BID (SEQ ID NO:8), HRK (SEQ ID NO:9), BOK (SEQ ID NO:10), and BIM (SEQ ID NO:11). Residues surrounded by a black box are identical. Residues surrounded by a gray box are homologous among BH3 domains. The code for the individual residues is A = alanine, C = cysteine, D = aspartic acid, E = glutamic acid, F = phenylalanine, G

At page 32, the paragraph encompassing lines 4-11 has been amended as follows:

Fig. 3(B) is a graphical representation of the results of an *in vitro* competition binding assay. Recombinant GST-Bcl-X_L was incubated with a BAD BH3 peptide (residues 143-168 of SEQ ID NO: 2) phosphorylated on Ser155 ("BAD BH3-P"), a BAD BH3 peptide (residues 143-168 of SEQ ID NO: 2) unphosphorylated on Ser155 ("BAD BH3"), or a BAK BH3 peptide

(residues 71-89; residues 1-20 of SEQ ID NO: 5) as a positive control, at the indicated concentrations. The reaction mixtures were then added to microtiter plates pre-coated with BAK BH3 peptide. The amount of bound GST-Bcl-X_L was determined by ELISA using an anti-GST primary antibody and a horse-radish peroxidase-conjugated anti-mouse IgG secondary antibody with ABTS as substrate.

IN THE CLAIMS:

The claims are amended as follows:

1. An isolated polypeptide comprising an amino acid sequence of a mutant Bcl-X_L/Bcl-2 Associated Cell Death Regulator polypeptide (BAD), or fragment of said isolated or synthetic polypeptide comprising a less than full-length amino acid sequence of said mutant BAD, wherein:

a) said isolated or synthetic polypeptide, or said fragment, contains a domain at least 75% homologous ~~substantially identical~~ to a BH3 domain of a naturally-occurring or wild-type mammalian BAD;

b) said amino acid sequence of said isolated or synthetic polypeptide, or said amino acid sequence of said fragment, does not have a serine at a position corresponding to position 118 of SEQ ID NO:1, said position in said amino acid sequence of said isolated or synthetic polypeptide, or said position in said amino acid sequence of said fragment, being identified by alignment of said amino acid sequence of said isolated or synthetic polypeptide, or said amino acid sequence of said fragment, to SEQ ID NO:1; and

c) said isolated or synthetic polypeptide, or said fragment, has cell death promoting activity.

2. The isolated or synthetic polypeptide, or fragment, of Claim 1, wherein the amino acid sequence of said mutant BAD, or of said fragment, is at least 75% homologous ~~substantially identical~~ to SEQ ID NO:1

13. The isolated or synthetic polypeptide, or fragment, of Claim 10, wherein said isolated or synthetic polypeptide binds Bcl-X_L and/or Bcl-2, or said fragment binds Bcl-X_L and/or Bcl-2, through said domain that is at least 75% homologous ~~substantially identical~~ to a BH3 domain of a naturally-occurring or wild-type mammalian BAD.